Synthetic Studies on Pyridomycin. III.[1] Chiral Synthesis of (2*R*,2*S*)-(−)-2,3-Dihydroxy-3-methylpentanoic Acid from Sugar Derivative

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The Grignard reaction of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**5**) with ethylmagnesium bromide yielded 3-*O*-benzyl-6-deoxy-5-*C*-ethyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) as a major product in 91% stereoselectivity. Hydrolysis of **6** followed by successive periodate oxidation and lithium aluminium hydride reduction gave 2-*O*-benzyl-5-deoxy-4-*C*-ethyl-D-arabinitol. Selective benzoylation of **9** followed by successive 3,4-*O*-isopropylidenation, debenzoylation, hydrogenolysis, and two-stage oxidation with periodate-hypoiodite afforded (4*R*,5*S*)-(+)-5-ethyl-2,2,5-trimethyl-1,3-dioxolane-4-carboxylic acid (**15**) in 24.6% overall yield from **5**. Hydrolysis of **15** gave (2*R*,3*S*)-(−)-2,3-dihydroxy-3-methylpentanoic acid. The acetonide **15** is usefull as a synthon for pyridomycin synthesis.

The structure of pyridomycin (**1**) contains (*Z*)-2-acyloxy-3-methyl-2-pentenoic ester (unit **A**) which corresponds to the unique exocyclic *s*-butylidene side chain moiety in the twelve-membered ring system.[2] For the total synthesis of pyridomycin, it was desirable for the precursor of **1** to contain an appropriate 2-*O*-acylated dihydroxy ester (unit **2**) derived from *threo*-2,3-dihydroxy-3-methylpentanoic acid such as structure **3**, since dehydration of unit **2** is expected to afford predominantly unit **A** in **1** by *trans*-elimination.[3]

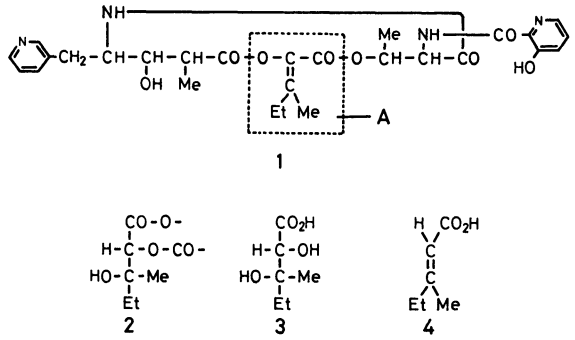

Fig. 1.

The (±)- and (−)-*threo*-2,3-dihydroxy-3-methylpentanoic acids have been prepared from (*E*)-3-methyl-2-pentenoic acid (**4**) by *cis*-hydroxylation[4,5] and by optical resolution of the (±)-*threo*-acid,[5] respectively. This synthetic method seems less promising since the isomerically pure key substance **4** can not be easily prepared on a large scale. On the other hand, a mixture of the *threo*- and *erythro*-dihydroxy acids has easily been prepared from ethyl 3-methyl-2,3-epoxypentanoate.[6,7] However, attempts to isolate the *threo*-isomer from the isomeric mixture have not yet been successful.

This paper presents a chiral synthesis of (2*R*,3*S*)-2,3-dihydroxy-3-methylpentanoic acid (**3**)[8] *via* its acetonide (2,3-*O*-isopropylidene derivative) **15** from 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**5**)[9,10] through the route shown in Fig. 2. In the first step, the desired product **6** in which the configuration of the C-5 carbon is identical with that of the C-3 carbon in the target compound **3**, was obtained in high stereoselectivity by the asymmetric Grignard reaction.[11–13] The isomerically pure acetonide **15** derived from **6** substantially contributed to the configurational assignment of **6**. The acetonide **15** is useful not only as a precursor for **3** but also as a synthon for synthesis of a precursor of **1**. This synthesis is advantageous for all the optically active diastereo- and enantio-isomers of **3**. the (3*R*)-epimer **3'** (Fig. 2), which has been established[5–8] to be an intermediate in the biosynthesis of isoleucine, will be synthesized *via* **6'** by the use of the ulose **5'** as a starting material instead of **5**. The enantiomer of **5** will be converted into the optical antipode of **3** which is also useful in the pyridomycin synthesis.

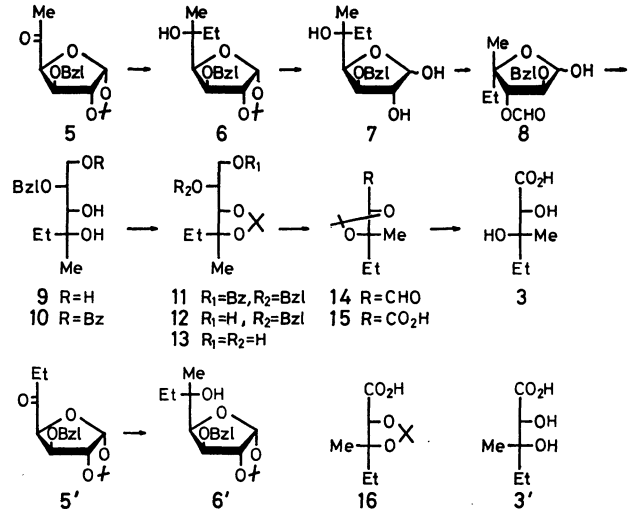

Fig. 2.

Results and Discussion

The Grignard reaction of **5** with an eight-fold excess of ethylmagnesium bromide in ether afforded a crystalline condensation product in 80.1% yield after recrystallization from pentane. A thorough examination of this product by PMR spectroscopy revealed that it is a *ca.* 91:9 mixture of the desired 3-*O*-benzyl-6-deoxy-5-*C*-ethyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) and its 5-epimer **6'**. Further purification of the product by recrystallization gave no isomerically pure major isomer **6**. For the PMR analysis a pure sample of **6** was isolated

from the product by silica gel column chromatography in a poor yield. A pure sample of the minor isomer **6'** was obtained by column chromatography of a product containing mainly **6'** (91%) prepared by the Grignard reaction of 3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptofuranos-5-ulos (**5'**)[10] and methylmagnesium iodide. The PMR spectra of **6** and **6'** showed a characteristic singlet at δ 1.15 and 1.26 ascribed to the methyl protons of each isomer, respectively. The assignment of the (5*S*)-configuration for **6** was rationalized on the basis of the results of asymmetric Grignard reactions of free carbonyl sugar derivatives reported by Wolfrom and Hanessian,[11] Inch,[12] and Inch *et al.*[13] The assumed configuration was verified by PMR study of the acetonide **15** derived from **6** (see below). Hydrolysis of **6** (the aforesaid isomeric mixture) in a boiling 50% aqueous acetic acid afforded free sugar in 92% yield, to which the furanose structure **7** was given, because it could be smoothly converted into the subsequent product **8**. Periodate oxidation of **7** gave 2-*O*-benzyl-5-deoxy-4-*C*-ethyl-3-*O*-formyl-D-arabinofuranose (**8**) in 87.6% yield after treatment by silica gel chromatography. The PMR spectrum of **8** showed signals in line with the furanose structure. Lithium aluminium hydride reduction of **8** in THF afforded 2-*O*-benzyl-5-deoxy-4-*C*-ethyl-D-arabinitol (**9**) as colorless prisms in 98.3% yield. This sample appeared to be isomerically homogeneous as judged from its PMR spectrum. Selective benzoylation of **9** with benzoyl chloride in pyridine gave the 1-*O*-benzoate **10** in 86.3% yield after being subjected to silica gel chromatography. Treatment of **10** with 2,2-dimethoxypropane containing a small amount of *p*-toluenesulfonic acid yielded 3,4-acetonide **11** in 96.6% yield. Debenzoylation of **11** with sodium methoxide afforded 2-*O*-benzyl-5-deoxy-4-*C*-ethyl-3,4-*O*-isopropylidene-D-arabinitol (**12**) in 81.7% yield after being subjected to chromatography. Hydrogenolysis of **12** followed by periodate oxidation of the resulting diol **13** gave the crude aldehyde **14** in 71.9% yield. The aldehyde was then oxidized with potassium hypoiodite[14] to afford the crystalline acetonide **15** in 79.2% yield (24.6% overall yield from **5**). The sample of **15** was shown to be isomerically homogeneous by its PMR spectrum.

Hill and Yan[7] reported on the acetonide **16** corresponding to (2*R*,3*R*)-(−)-2,3-dihydroxy-3-methylpentanoic acid (**3'**).[5,7] A comparison of the PMR data of **15** with those of **16** shows significant differences between the chemical shifts of the corresponding 5-methyl and 5-ethyl protons on the 1,3-dioxolane ring of each acetonide (see Table). Thus acetonide **15** was proved to be the (5*S*)-epimer of **16**, the (5*S*)-configuration of **6** being verified.

Treatment of **15** with 50% trifluoroacetic acid yielded the title compound **3** as a syrup in quantitative yield. The PMR spectrum showed signals in line with the structure. The hydroxy acid **3** exhibited a weak positive CD Cotton effect at 235 nm in addition to the strong negative Cotton effect at 205 nm in water. The result is also consistent with the (2*R*)-configuration of **3**.[5,15]

Experimental

Melting points were determined on a micro hot-stage and are uncorrected. PMR spectra were taken on a Varian A-60D spectrometer using TMS and DSS as internal standards. Specific rotations were determined with a Zeiss Photoelectric Polarimeter. TLC and column chromatography were performed in Wakogel B-5 and C-200, respectively. Concentration was carried out under reduced pressure below 40 °C.

3-O-Benzyl-6-deoxy-5-C-ethyl-1,2-O-isopropylidene-α-D-glucofuranose (6). The starting material, 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**5**)[9,10] was prepared in 91% yield by Jones oxidation[10] of 3-*O*-benzyl 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[9,10,12] which was derived *via* 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[16] from 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[17] in 83% overall yield. A solution of **5** (30 g, 0.1026 mol) in dry ether (900 ml) was added dropwise under stirring to an ether solution of ethylmagnesium bromide prepared from magnesium turnings (20.0 g, 0.8235 mol) and ethyl bromide (61.8 ml, 0.8227 mol) in dry ether (900 ml). The mixture which was stirred at room temperature for 3 h was treated with a cold saturated aqueous NH_4Cl solution (800 ml) under cooling. The aqueous layer was extracted with ether, and the combined ether layer were washed with saturated aqueous NaCl solution, dried and evaporated to afford a pale yellow crystalline solid (32.7 g, mp 51—60 °C). The solid was recrystallized from pentane to give needles of the condensation product (26.8 g, 80.1%, mp 64—64.5 °C) which was shown by PMR analysis to be a 91:9 mixture of the title compound **6** and its 5-epimer **6'**. The product (1 g) was recrystallized from pentane to afford colorless needles (0.79 g); mp 64—65 °C, $[\alpha]_D^{20}$ −68° (*c* 2.06, $CHCl_3$). The PMR spectrum showed no appreciable change in the proportion of **6** to **6'**. The product (1.00 g) was chromatographed on silica gel (180 g) with benzene–ethyl acetate (6:1). By PMR inspection, the effluent containing the pure isomer **6** was collected in the fore-run, giving a pure sample (82 mg, 8.2%) of **6**: colorless needles, mp 64.3—65 °C; $[\alpha]_D^{20}$ −72° (*c* 0.6, $CHCl_3$); δ ($CDCl_3$) 0.92 (t, 3H, 5-$CH_2\underline{CH_3}$, J=7 Hz, 1.15 (s, 3H, H-6), 1.34 and 1.50 [each s, 3H, C-$(CH_3)_2$], 1.72 (m, 2H, 5-$C\underline{H_2}CH_3$), 3.71 (s, 1H, OH), 4.01

Table 1. Comparison of 60 MHz PMR data (δ, $CDCl_3$) of **15** with the published PMR data (60 MHz, δ, $CDCl_3$)[7] of (4*R*,5*R*)-5-ethyl-2,2,5-trimethyl-1,3-dioxolane-4-carboxylic acid (**16**)

Substance	5-$CH_2\underline{CH_3}$ (t, 3H)	5-CH_3 (s,3H)	CH_3–C–CH_3 (each s, 3H)		5-$C\underline{H_2}CH_3$ (m,2H)	H-4 (s, 1H)	COOH (s, 1H)
15	1.02 (J=7 Hz)	1.23	1.41	1.57	1.80	4.42	9.18
16	0.94 (J=6 Hz)	1.44	1.41	1.52	1.68	4 41	9.91

and 4.18 (each d, H-3, H-4, $J_{3,4}$=3 Hz),** 4.69 (d, 1H, H-2, $J_{1,2}$=4 Hz), 4.57 and 4.78 (each d, each 1H, O-C$\underline{H}_2$Ph, J_{gem}=12 Hz),** 6.11 (d, 1H, H-1), and 7.44 (s, Ph).

Found: C, 67.05; H, 8.20%. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13%.

3-O-Benzyl-6-deoxy-5-C-ethyl-1,2-O-isopropylidene-α-D-idofuranose (6′). 3-*O*-Benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptofuranos-5-ulose (**5′**)[10] (475 mg) was allowed to react with an eight-fold excess of methylmagnesium iodide in ether (29 ml) at room temperature for 3 h. Work-up as in the preparation of **6** followed by purification of the crude product through a silica gel column (27 g) with benzene–ethyl acetate (6: 1) afforded a syrup of the condensation product (471 mg, 94.1%) which was shown by PMR analysis to be a 91: 9 mixture of **6′** and **6**. The sample (422 mg) was again chromatographed on silica gel (76 g) with the same solvent system to give a pure sample (90 mg, 21.4%) of **6′** as colorless syrup: $[\alpha]_D^{19}$ −58° (*c* 1.0, $CHCl_3$); δ ($CDCl_3$) 0.92 (t, 3H, 5-$CH_2C\underline{H}_3$, *J*=7 Hz), 1.26 (s, 3H, H-6), 1.33 and 1.49 [each s, 3H, $C(CH_3)_3$], *ca.* 1.5 (m, 2H, 5-C$\underline{H}_2CH_3$), 3.40 (s, 1H, OH), 4.00 and 4.18 (each d, H-3, H-4, $J_{3,4}$=3 Hz),** 6.69 (d, 1H, H-2, $J_{1,2}$=4 Hz), 4.57 and 4.78 (each d,OC$\underline{H}_2$Ph, J_{gem}=11.5 Hz),** 6.11 (d, 1H, H-1), and 7.44 (s, 5H, Ph).

Found: C, 66.76; H, 8.13%. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 7.91%.

2-O-Benzyl-5-deoxy-4-C-ethyl-D-arabinitol (9). Treatment of the Grignard reaction product (10.0 g) containing *ca.* 91% of **6** with 50% aqueous acetic acid (60 ml) at 115 °C for 6 h, followed by evaporation afforded a brown syrup, which was dissolved in ethyl acetate (200 ml). The solution was washed successively with saturated $NaHCO_3$ and saturated NaCl solutions, dried and evaporated. The residual pale brown syrup (10.5 g) was chromatographed on silica gel (300 g) with benzene–ethyl acetate (1: 1) to give 3-*O*-benzyl-6-deoxy-5-*C*-ethyl-D-glucofuranose (**7**) (8.06 g, 92%). A sample of the free sugar **7** (7.96 g) was dissolved in acetone (240 ml) and treated with a solution of sodium metaperiodate (12.06 g) in water (120 ml) at room temperature for 3 h. A solution of the periodate (6.03 g) in water (60 ml) was added to the reaction mixture, which was stirred at room temperature overnight and filtered. Acetone was removed from the filtrate by evaporation and the aqueous residue was extracted with ethyl acetate. The extract was washed with saturated NaCl solution, dried and evaporated. The residual syrup (7.64 g) was chromatographed on silica gel (300 g) with benzene–ethyl acetate (6: 1) to afford a colorless syrup of 2-*O*-benzyl-5-deoxy-4-*C*-ethyl-3-*O*-formyl-D-arabinofuranose (**8**) as an anomeric mixture, yield 6.92 g (87.6%); δ ($CDCl_3$) 0.96 (dt, 3H, 4-$CH_2C\underline{H}_3$), 1.36 and 1.45 (each s, 3H, H-5), 1.76 (m, 2H, 4-C$\underline{H}_2CH_3$), 3.8—4.2 (br, 2H, H-2 and OH), 4.78 (d, 2H, OC$\underline{H}_2$Ph), 5.3—5.6 (m, 2H, H-1 and H-3), 7.48 (s, 5H, Ph), and 8.25 (s, 1H, OC$\underline{H}$O). A sample of **8** (5.56 g, 19.84 mmol) was dissolved in dry THF (209 ml) and cooled in an ice-bath. Powdered $LiAlH_4$ (1.50 g, 39.67 mmol) was added slowly to the stirred solution and then refluxed for 6 h. Ethyl acetate (150 ml) and water (5 ml) were added to the cooled reaction mixture and stirred at room temperature overnight. The mixture was filtered and the filter cake was washed with ethyl acetate. The filtrate and washings were combined and washed with saturated NaCl solution, dried and evaporated to give **9** as colorless needles (4.96 g, 98.3%). Recrystallization from ether–petroleum ether afforded an analytical sample: prisms, mp 58—59 °C; $[\alpha]_D^{23}$ −60° (*c* 1.00, $CHCl_3$); δ ($CDCl_3$) 0.96 (t, 3H, 4-$CH_2C\underline{H}_3$), 1.13 (s, 3H, 5-H), 1.56 (q, 2H, 4-C$\underline{H}_2$-CH_3), 2.86 (s, 3H, OH), 3.51 (d, 1H, H-3, $J_{2,3}$=2 Hz), 3.6—4.2 (m, 3H, H-1,1′ and H-2), 4.48 and 4.75 (each d, 2H, OC$\underline{H}_2$Ph, J_{gem}=11 Hz),** and 7.30 (s, 5H, Ph).

Found: C, 66.25; H, 8.63%. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72%.

1-O-Benzoyl-2-O-benzyl-5-deoxy-4-C-ethyl-D-arabinitol (10). Benzoyl chloride (6.17 ml, 53.0 mmol) was added to a solution of **9** (12.26 g, 48.19 mmol) in dry pyridine (245 ml) cooled at −10 °C. The mixture was allowed to stand at 4 °C for 24 h and then poured into cold water (200 ml) and extracted with chloroform (300 ml×3). The concentrated extract was diluted with chloroform (300 ml); this was washed with 50% aqueous $KHSO_4$ solution, saturated $NaHCO_3$ and saturated NaCl solutions successively, dried and evaporated to yield a syrup (18.73 g), which was chromatographed on silica gel (360 g) with benzene–ethyl acetate (6: 1) to afford a colorless syrup of **10** (14.9 g, 86.3%): $[\alpha]_D^{20}$ −19° (*c* 1.04, $CHCl_3$); IR $(CCl_4)_{max}$ 3500 (OH) and 1710 cm^{-1} (ester); δ ($CDCl_3$) 0.92 (t, 3H, 4-$CH_2C\underline{H}_3$, *J*=7 Hz), 1.16 (s, 3H, H-5), 1.66 (m, 2H, 4-C$\underline{H}_2$-CH_3), 3.30 (s, 2H, OH), 3.62 (d, 1H, H-3, $J_{2,3}$=2 Hz), 4.22 (dt, 1H, H-2, $J_{1,2}$=5.5 Hz), 4.79 (d, 2H, H-1), 4.74 and 5.00 (each d, 2H, OC$\underline{H}_2$Ph),** 7.48 (s, 5H, OC$H_2\underline{Ph}$), 7.60 (m, 3H, benzoyl), and 8.26 (m, 2H, benzoyl).

Found: C, 70.49; H, 7.20%. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31%.

1-O-Benzoyl-2-O-benzyl-5-deoxy-4-C-ethyl-3,4-O-isopropylidene-D-arabinitol (11). A solution of **10** (14.90 g, 41.57 mmol) and *p*-toluenesulfonic acid (515 mg) in 2,2-dimethoxypropane (204 ml) was kept at room temperature for 2 h and then diluted with ether (500 ml). The mixture was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried and evaporated to afford the crude acetonide **11** (16.00 g, 96.6%). Analytical sample of **11** was obtained by chromatograpy of the crude **11** through a silica gel column with benzene–ethyl acetate (12: 1): $[\alpha]_D^{21}$ +29° (*c* 1.03, $CHCl_3$); IR $(CCl_4)_{max}$ 1710 cm^{-1} (ester); δ ($CDCl_3$) 0.98 (t, 3H, 4-$CH_2C\underline{H}_3$, *J*=7 Hz), 1.24 (s, 3H, H-5), 1.40 and 1.51 [each s, 3H, $C(CH_3)_3$], 1.66 (m, 2H, 4-C$\underline{H}_2$-CH_3), 3.8—4.8 (m, 4H, H-3, H-2, and H-1), 4.91 (s, 2H, OC$\underline{H}_2$Ph), 7.46 (d, 5H, OCH_2Ph), 7.64 (m, 3H, benzoyl), and 8.22 (m, 2H, benzoyl).

Found: C, 72.10; H, 7.61%. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59%.

2-O-Benzyl-5-deoxy-4-C-ethyl-3,4-O-isopropylidene-D-arabinitol (12). The crude acetonide **11** (16.00 g) was dissolved in dry methanol (320 ml). A solution of 2.5 M sodium methoxide in methanol was added under ice-cooling and kept at room temperature for 1 h. The resulting mixture was poured into ice–water (230 ml) and extracted with chloroform (200 ml×3). The extract was washed with saturated NaCl solution, dried and evaporated. The residual syrup (16.38 g) was chromatographed on silica gel (500 g) with benzene–ethyl acetate (6: 1) to afford a colorless syrup of **12** (9.66 g, 81.7%): $[\alpha]_D^{22}$ +35° (*c* 1.14, $CHCl_3$); δ ($CDCl_3$) 1.00 (t, 3H, 4-CH_2-$C\underline{H}_3$, *J*=7 Hz), 1.26 (s, 3H, 5-H), 1.38 and 1.51 [each s, 3H, $C(CH_3)_2$], 1.60 (m, 2H, 4-C$\underline{H}_2CH_3$), 3.4—4.2 (m, 4H, H-3, H-2, and H-1), 4.77 and 5.10 (each d, 2H, OC$\underline{H}_2$Ph, J_{gem}= 12 Hz),** and 7.50 (s, 5H, Ph).

Found: C, 69.09; H, 8.74%. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.

(4R,5S)-(+)-5-Ethyl-2,2,5-trimehyl-1,3-dioxolane-4-carboxylic Acid (15). A solution of **12** (2.30 g) in methanol (70 ml) was stirred with palladium black for 1 h under bubbling with hydrogen gas. The filtered solution was evaporated to a colorless syrup of 5-deoxy-4-*C*-ethyl-3,4-*O*-isopropylidene-D-arabinitol (**13**) (1.60 g, 100%) which appeared to be homogeneous on TLC with benzene–ethyl acetate (1: 1). A sample of **13** (6.70 g, 32.8 mmol) was dissolved in acetone (200 ml)

** The chemical shifts for the protons of system AB were calculated.

and treated with a solution of sodium metaperiodate (14.04 g, 65.6 mmol) in water (140 ml). After being stirred in a dark place at room temperature for 1 h, the reaction mixture was filtered and the acetone was removed by concentration of the filtrate. The resulting aqueous residue was extracted with chloroform (100 ml×2). The extracts were washed with saturated NaCl solution, dried and evaporated to give (4*R*, 5*S*)-5-ethyl-2,2,5-trimethyl-1,3-dioxolane-4-carbaldehyde (**14**) (4.07 g, 71.9%) as a colorless liquid; δ($CDCl_3$) 1.02 (t, 3H, 5-$CH_2C\underline{H}_3$, J=7 Hz), 1.20 (s, 3H, 5-CH_3), 1.42 and 1.58 [each s, 3H, $C(CH_3)_2$], 1.74 (m, 2H, 5-$C\underline{H}_2CH_3$), 4.22 (d, 1H, H-4, $J_{5,CHO}$=2 Hz), and 9.98 (d, 1H, CHO). The aldehyde **14** (4.06 g, 23.6 mmol) was dissolved in dioxane (100 ml). The solution was diluted with water (37 ml), and a solution of K_2CO_3 (20.55 g, 148.7 mmol) and $KHCO_3$ (14.89 g, 148.7 mmol) in water (160 ml) was added. A solution of iodine (17.62 g, 69.4 mmol) and KI (23.04 g, 138.8 mmol) in water (20 ml) was added, and the mixture was stirred at room temperature for 2 h. The cooled mixture was reduced by the addition of solid sodium thiosulfate. The resulting colorless solution was washed with ether to remove the unchanged aldehyde and impurities. The aqueous solution was made acid (pH 2—3) with 10% sulfuric acid under ice-cooling, and immediately extracted with chloroform (100 ml×3). The extracts were washed with saturated NaCl solution, dried and evaporated to yield colorless crystals of **15** (3.52 g, 79.2%), whose PMR spectrum showed no signals indicating the presence of the (4*R*)-epimer **16**. The crude crystals (20 mg) were subjected to sublimation at 49 °C (bath temp) under reduced pressure (1 Torr) to afford a pure sample (18.8 mg) as hygroscopic colorless needles: mp 46.5—49 °C (subl); $[\alpha]_D^{20}$ +26° (*c* 0.84, $CHCl_3$).

Found: C, 57.58; H, 8.44%. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57%.

(2R3,S)-(−)-2,3-Dihydroxy-3-methylpentanoic Acid (3). A sample of **15** (200 mg) was dissolved in 50% aqueous trifluoroacetic acid (2 ml). After being kept at room temperature for 4 h, the solution was evaporated to afford **3** as a pale yellow syrup. The crude acid (217 mg) was purified by silica gel chromatography with chloroform–methanol–acetic acid (80: 10: 1) and the resulting colorless syrup was again chromatographed with chloroform–ethyl acetate (1: 1) to give a pure sample of **3** (155 mg, 98.2%): $[\alpha]_D$ −28°, $[\alpha]_{436}$ −63°, $[\alpha]_{365}$ −106° (*c* 1.48, $CHCl_3$, at 20°); $[\alpha]_D$ −16°, $[\alpha]_{436}$ −34°, $[\alpha]_{365}$ −55° (*c* 1.32, H_2O, at 20°); CD, $[\theta]_{235}$ +290 and $[\theta]_{205}$ −5460 (*c* 0.115, H_2O); δ (D_2O, DSS) 0.90 (t, 3H, H-5, J=7 Hz), 1.21 (s, 3H, 3-CH_3), *ca.* 1.6 (m, 2H, H-4), 4.10 (s, 1H, H-2), and 4.62 (s, DOH); δ ($CDCl_3$) 0.94 (t, 3H, H-5, J=7 Hz), 1.27 (s, 3H, 3-CH_3), *ca.* 1.6 (m, 2H, H-4), 4.07 (s, 1H, H-2), and 5.82 (s, 3H, CO_2H, OH).

Found: C, 48.47; H, 8.35%. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16%.

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